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ORIGINAL ARTICLE

The efficacy of panitumumab in refractory metastatic colorectal cancer: A meta-analysis

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Summary

Purpose: *Panitumumab, an anti-epithelial growth factor receptor (EGFR) antibody, has been known to be effective treatments for wild-type KRAS metastatic colorectal cancer (mCRC). However, the efficacy of panitumumab for refractory mCRC remains controversial. Thus, we performed this meta-analysis to clarify and evaluate the effectiveness of panitumumab in patients with refractory mCRC.*

Methods: *PubMed, Cochrane and Embase were searched up to October 2018 using appropriate key words. Only randomized controlled trials (RCTs) were included in the qualified studies. Odds ratio (OR) along with 95% confidence interval (95% CI) were utilized for main outcome analysis.*

Results: *A total of 7 RCTs were included in this analysis. Overall survival (OS, OR=1.01, 95% CI 0.81-1.27; p=0.90) and progression free survival (PFS, OR =0.78, 95% CI 0.62-1.00; p=0.05) were not significantly different in mCRC patients pretreated with panitumumab, but the pooled OR for overall response rate (ORR) was 3.71 (95% CI 1.34-10.31;p=0.01), indicating that panitumumab improved the ORR. Moreover, subgroup analysis showed that patients treated with panitumumab plus irinotecan-based chemotherapy did not achieve any benefit in PFS (OR=0.91, 95% CI 0.68-1.22; p=0.53) or OS (OR=0.93, 95% CI 0.79-1.09; p=0.36) than controls. The results also indicated that the combination chemotherapy with either panitumumab or cetuximab was comparable in efficacy in terms of PFS (OR=0.80, 95% CI 0.62-1.04; p=0.10) and OS (OR=1.28, 95% CI 0.72-2.27, p=0.40).*

Conclusions: *The current analysis indicates that panitumumab was not associated with survival benefit but ORR was improved among pre-treated mCRC patients. Future investigations are needed to identify relevant biomarkers in selected patients that would most likely benefit from panitumumab therapy for refractory mCRC.*

Key words: *panitumumab, metastatic colorectal cancer, pretreated patients, meta-analysis*

Introduction

Colorectal cancer (CRC) is a common malignancy with a high cancer-related mortality around the world, and half of CRC patients will develop metastatic disease [1]. For advanced cases, further treatments after failure of initial therapy should be employed. Along with improvements in systemic chemotherapy in advanced metastatic colorectal cancer (mCRC), the emergence of molecular-targeted agents has offered clinical benefits in the treatment of pretreated advanced mCRC [2-4].

The epidermal growth factor receptor (EGFR) is overexpressed in CRC [5], and has been regarded as a molecular therapeutic target by activating various signaling pathways that regulate cell proliferation [6]. It has been well-established that panitumumab, a fully humanized monoclonal antibody against EGFR, achieves survival benefit in patients

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with mCRC [7]. However, panitumumab appears to have different results when compared to different chemotherapeutics either alone or in addition to others to treat the mCRC.

The ASPECCT trial compared the efficacy of panitumumab and cetuximab and showed that the overall survival (OS) of mCRC patients who were refractory or intolerant to chemotherapy and treated with panitumumab was similar to that of patients treated with cetuximab [8]. Moreover, panitumumab plus irinotecan-based chemotherapy showed beneficial results compared with the addition of panitumumab to oxaliplatin-based chemotherapy [9,10].

Today, there are still conflicting results over the therapeutic efficacy of panitumumab for mCRC patients who have failed initial therapy. The objective of this meta-analysis was to assess the efficacy of panitumumab in pre-treated mCRC patients.

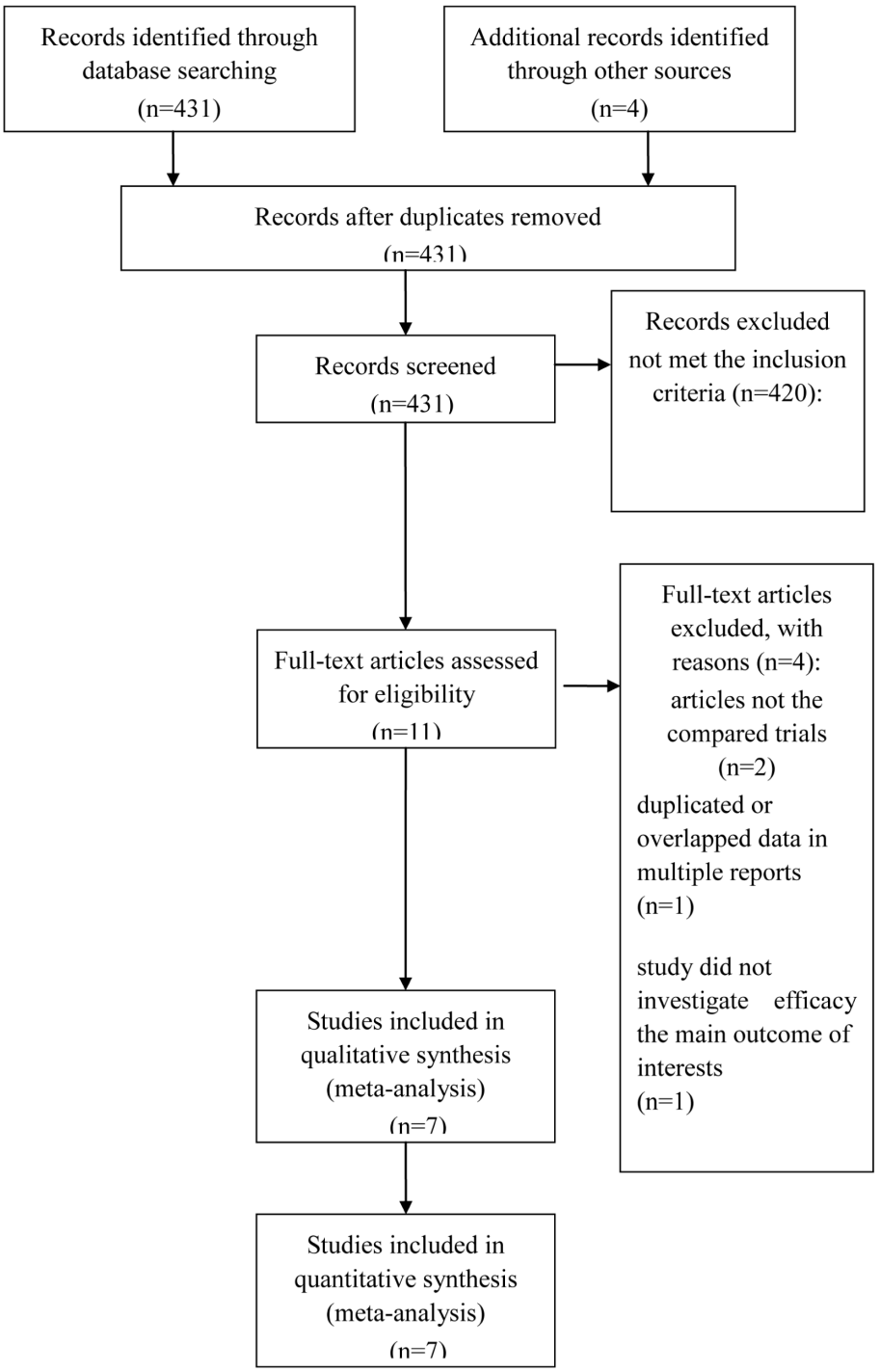

Figure 1. PRISMA flow chart of the selection process to identify studies eligible for pooling.

Table 1. Detailed information of included studies

Study,Year	*Treatment regimen*		*Patients number*		*Age(years)*	
	Study arm	*Comparative arm*	*Study arm*	*Comparative arm*	*Study arm*	*Comparative arm*
Shitara, 2016	FOLFIRI plus panitumumab	FOLFIRI plus bevacizumab	59	58	62	64
Jerzak, 2017	panitumumab monotherapy	cetuximab plus irinotecan	803	278	64	61
Hecht 2014	FOLFIRI plus panitumumab	FOLFIRI plus bevacizumab	91	91	62	58
Kim 2016	panitumumab plus best supportive care	best supportive care	189	188	62	60
Hayashi, 2018	panitumumab	cetuximab	44	178	/	/
Peeters, 2015	FOLFIRI plus panitumumab	FOLFIRI alone	208	213	60	60
Yamaguchi, 2016	Panitumumab plus irinotecan	Cetuximab plus irinotecan	42	107	62	63

Methods

Search strategy

We searched electronic databases including PubMed, Embase, and Cochrane from the study inception to October 2018 to identify all eligible studies. The process was to find all articles with the keywords: "panitumumab" AND "metastatic colorectal cancer" AND "EGFR", AND "pretreated patients" and relevant Medical Subject Heading (MeSH) terms were used during the literature search. Literature was also searched using reference lists and materials.

Eligibility criteria

Articles that complied to the following inclusion criteria were included in this analysis: (1) randomized control trials (RCTs); (2) mCRC patients who had received prior chemotherapy; (3) trials comparing the efficacy of panitumumab with chemotherapy; (4) at least one of the following outcome measures was reported: OS, PFS, and ORR and hazard ratios (HRs) with corresponding 95% CI (Cis); (5) the full texts were available.

Quality assessment

Two investigators assessed the quality of the retrieved studies independently. Study quality was justified using the Cochrane Collaboration's "Risk of bias" tool.

Data extraction

Two authors separately extracted the relevant data from each trial. Disagreement was settled through discussion. From each of the eligible studies, the main categories were based on the following: name of first author, year of publication, patient number, mean age, treatment regimen, and main outcomes. We extracted the corresponding odds ratios (ORs) with 95%CI to describe the endpoints of interest.

Statistics

The Review Manager version 5.3 software (Revman; The Cochrane collaboration Oxford, United Kingdom) was utilized to perform all statistical analyses. To assess the heterogeneity of studies and determine the model for analysis (the random-effects model or the fixed-effects model), I^2 tests and x^2 test were conducted [11]. The fixed-effects model was used if heterogeneity was insignificant ($I^2 \leq 50\%$). If the source of heterogeneity was not insignificant ($I^2 > 50\%$) or uncertain, we used the random-effects model for further analysis [12]. P value <0.05 showed statistical significance. Findings of our meta-analysis were performed in forest plots.

Results

Overview of literature search and study characteristics

A total of 431 studies were screened for eligibility. During preliminary screening of abstracts and titles, 420 studies were eliminated, leaving 11 publications for further assessment, but some did not provide enough detail of outcomes of the two approaches. Finally, a total of 7 RCTs [13-19] were eligible in the meta-analysis (Figure 1). All included studies were based on moderate to high quality evidence. Table 1 provides a brief description of these 7 studies.

Clinical and methodological heterogeneity

Pooled analysis of PFS comparing panitumumab versus chemotherapy

The pooled results from 6 studies showed that the PFS of the chemotherapy group was compara-

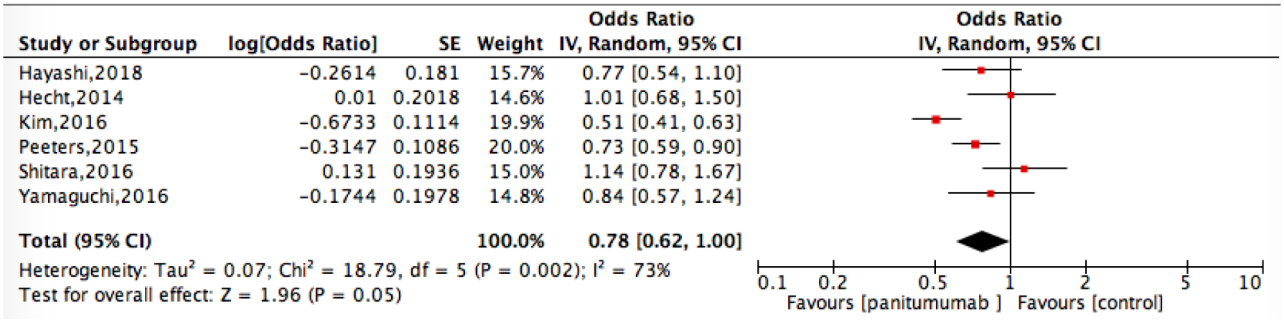

Figure 2. The effect of comparing panitumumab-based chemotherapy on PFS.

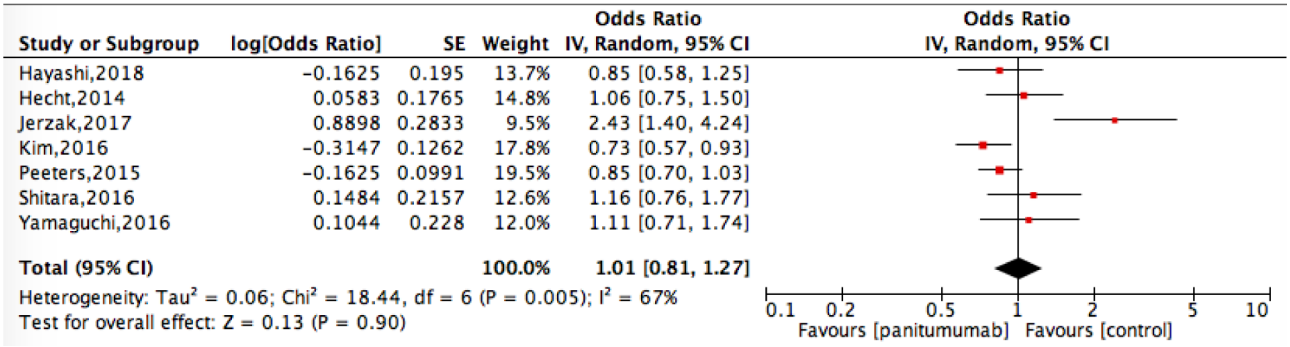

Figure 3. The effect of panitumumab-based chemotherapy to chemotherapy on OS.

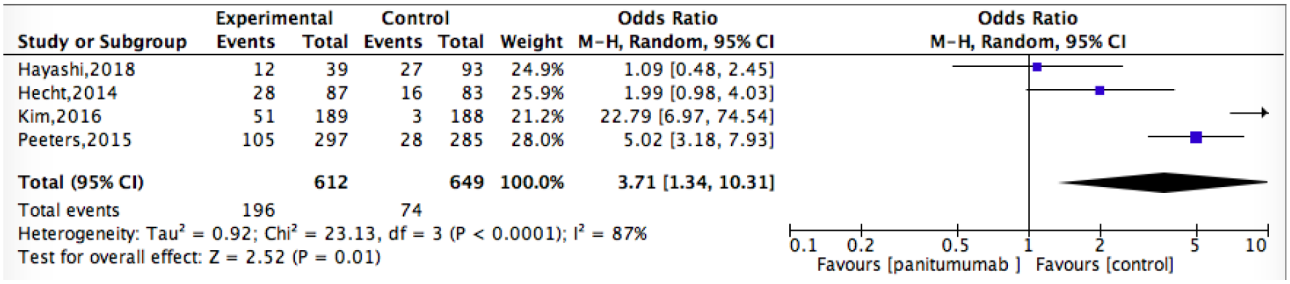

Figure 4. The effect of panitumumab-based chemotherapy on ORR.

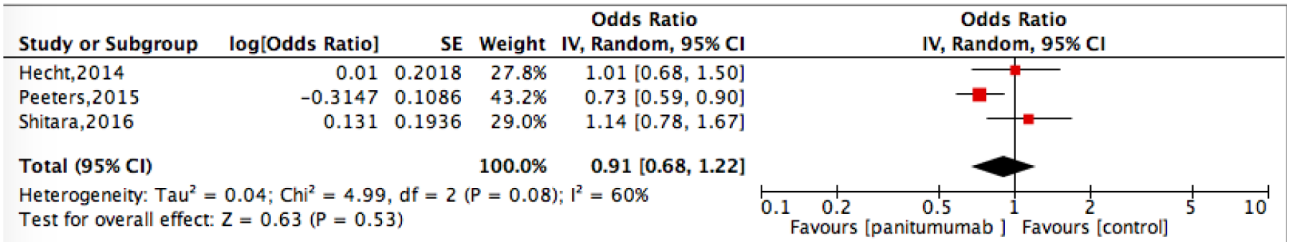

Figure 5. Pooled analysis of PFS comparing panitumumab versus irinotecan-based chemotherapy.

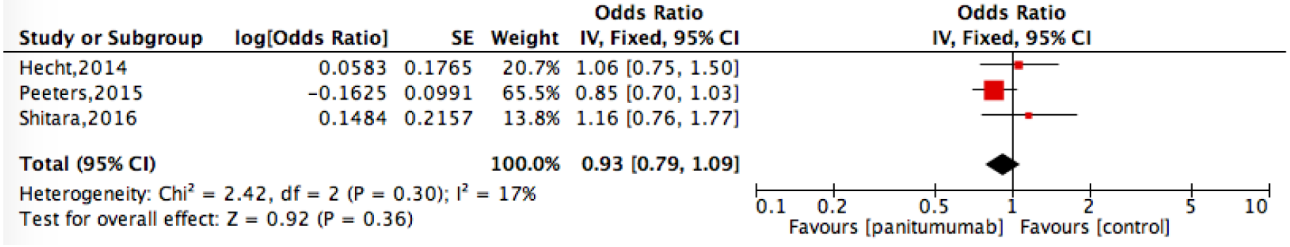

Figure 6. Pooled analysis of OS comparing panitumumab versus irrinotecan-based chemotherapy.

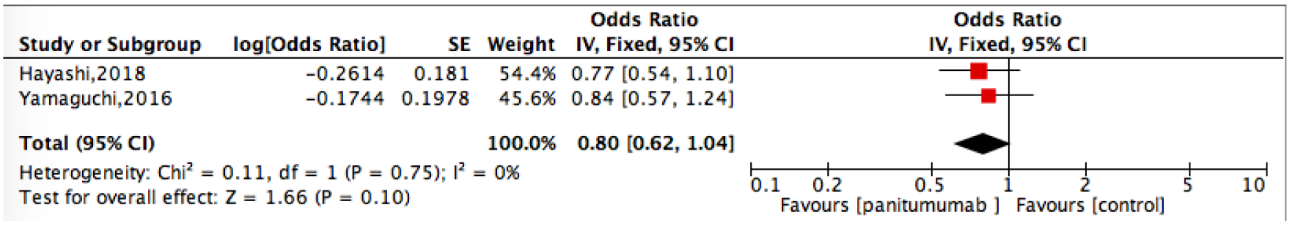

Figure 7. Pooled analysis of PFS comparing panitumumab-based chemotherapy versus cetuximab-based chemotherapy.

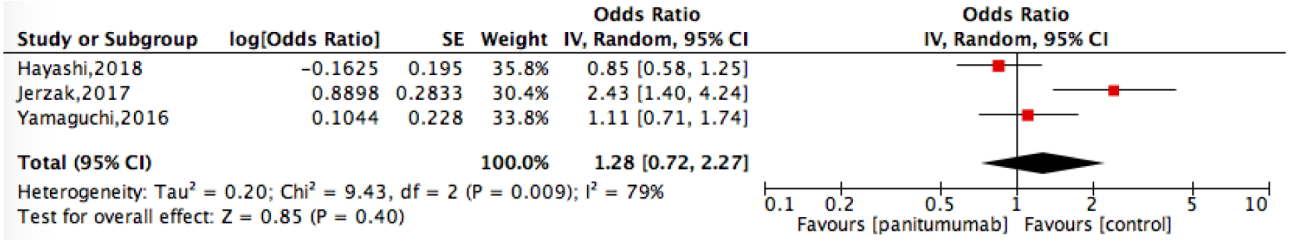

Figure 8. Pooled analysis of OS comparing panitumumab-based chemotherapy versus cetuximab-based chemotherapy.

ble with the panitumumab group (OR=0.78, 95% CI 0.62-1.00; p=0.05) (Figure 2).

Pooled analysis of OS comparing panitumumab versus chemotherapy

In the analysis of OS, all studies were included, and the data are shown in Figure 3. The results showed no significant difference in OS between the panitumumab group and the chemotherapy group (OR=1.01, 95% CI 0.81-1.27; p=0.90).

Pooled analysis of ORR comparing panitumumab versus chemotherapy

The pooled ORR data showed a significant difference between the two groups (OR=3.71, 95% CI 1.34-10.31; p=0.01). i.e. significantly increased ORR was found in the panitumumab group (Figure 4).

Subgroup analysis of patients treated with panitumumab plus irinotecan-based chemotherapy

Subgroup analysis showed that patients treated with panitumumab plus irinotecan-based chemotherapy did not differ significantly in PFS *versus* the controls (OR=0.91, 95% CI 0.68-1.22; p=0.53) (Figure 5) and OS (OR=0.93, 95% CI 0.79-1.09; p=0.36) (Figure 6).

Subgroup analysis of patients treated with panitumumab-based chemotherapy vs cetuximab-based chemotherapy

The pooled data showed no significant difference in PFS (OR=0.80, 95% CI 0.62-1.04; p=0.10) (Figure 7) and OS (OR=1.28, 95% CI 0.72-2.27; p=0.40) (Figure 8) between panitumumab and cetuximab for pretreated advanced mCRC patients.

Discussion

Chemotherapeutic agents have significantly contributed to survival improvement, disease control and quality of life in patients with advanced-stage cancer [20,21]. Panitumumab can directly bind to EGFR, and has been used to treat wild-type (WT) *KRAS* patients who have disease progression after the standard treatment [22,23]. This monoclonal antibody is commonly used with the addition to back-bone standard cytotoxic chemotherapy including fluorouracil and leucovorin as first- or second-line chemotherapy, which is based on positive outcomes from previous trials [24]. Yet, the efficacy of panitumumab still remains under investigation.

According to this meta-analysis, patients treated with panitumumab were non-inferior to patients treated with chemotherapy concerning survival. Based on previous findings, the 20100007 study [16], a phase 3 trial evaluating panitumumab plus best supportive care vs best supportive care in chemorefractory wild-type *KRAS* or *RAS* mCRC. has demonstrated the positive value of wild-type *KRAS* exon 2 for response in mCRC patients receiving panitumumab monotherapy. However, there is still a substantial proportion of wild-type *KRAS* exon 2 mCRC patients who are unlikely to benefit from panitumumab; thus, patient selection needs to be further refined. The results from both prospective and retrospective studies provide support to the use of panitumumab in wild-type *RAS* mCRC

patients [18]. Previous studies found that panitumumab plus FOLFIRI compared with FOLFIRI alone in the wild-type *RAS* mCRC group *versus* the wild-type *KRAS* exon 2 mCRC group achieved PFS and OS benefit. Conversely, patients with wild-type *KRAS* exon 2 but with other *RAS* mutations did not respond to panitumumab plus FOLFIRI [25-27].

Cetuximab, like panitumumab, was treated as a chimeric monoclonal antibody which is directed against *EGFR* [28]. Although both cetuximab and panitumumab have been used in wild-type *RAS* mCRC patients who have failed initial therapy [29,30], the optimal use of these agents either alone or in combination with chemotherapy is still under debate. In this meta-analysis, subgroup analysis demonstrated no benefit of panitumumab *versus* cetuximab for pretreated advanced mCRC in terms of survival. These findings can be viewed with caution: Firstly, the precise biological mechanisms differ between antibodies. Panitumumab has 3- to 8-fold higher affinity than the human murine chimeric monoclonal antibody cetuximab for targeting *EGFR* [30]. This differential pharmacokinetics may be associated with the difference in efficacy between the two antibodies. Secondly, toxicity induced by different anti-EGFR antibodies and chemotherapy affected post-progression therapy, which can be associate with the risk of death [31].

Regarding the ORR, our results showed that panitumumab led to significantly higher ORR in mCRC patients. In the Sotelo's study [32], the ORR for wild-type *RAS* panitumumab group was 41%, which is one of the highest rates in the second-line therapy. In patients receiving panitumumab, the tumor response was dramatic and the likelihood of achieving ≥30% reduction in tumor dimensions within 8 weeks of treatment was high, which should be considered during decision-making for second-line treatment.

Our study has several limitations. First, as this study was a study-level meta-analysis because of the lack of patient-level data, an imbalance existed among the included studies which might affect the results, even though all the included studies were RCTs. Second, patients with different *EGFR* and *RAS* mutations might have differential responses to panitumumab treatment. Future research should aim to identify subgroup of patients who are more likely to benefit from panitumumab through identification and validation of biomarkers.

In summary, the current study indicates that panitumumab was not associated with either OS or PFS benefit, but significantly increased ORR among pre-treated mCRC patients. Development in the therapy of mCRC patients who have disease progression after failure of initial therapy have led to a paradigm of "personalized" medicine in oncology, at least in selected patients with driver gene mutations such as *EGFR* mutations, which need to be explored in the future.

Conflict of interests

The authors declare no conflict of interests.

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